DEFENSE HEALTH AGENCY
NATIONAL CAPITAL REGION MEDICAL DIRECTORATE
8955 WOOD ROAD, BUILDING 1, FLOOR 9
BETHESDA, MARYLAND 20889-5628

JUL 25 2018

Dr. Remington Nevin
MuckRock
DEPT MR 22301
PO Box 55819
Boston, MA 02205-5819

Re: Freedom of Information Act (FOIA) Appeal 2016-010

Dear Dr. Nevin:

On June 23, 2015, you requested under the Freedom of Information Act (FOIA), the Defense Health Agency (DHA or "agency") provide: "Minutes from all 'Epi-Chiefs' teleconferences hosted by the Armed Forces Health Surveillance Center (AFHSC) from July 1, 2012 to the date of processing of this request which reference the antimalarial drug mefloquine (also known as Lariam)."

On January 12, 2016, the DHA FOIA office denied the request, citing 5 U.S.C. § 552(b)(5), which exempts internal records that are deliberative in nature and part of the decision-making process, containing opinions and recommendations.

You filed an appeal to FOIA 2016-010 on Feb 19, 2016. You sent additional appeal inquiries on May 24, June 1, and August 16, 2016, respectively. The appeal is granted in part. The Armed Forces Health Surveillance Center provided the requested "Epi-Chiefs minutes from May 3, 2018 and October 23, 2014 which reference mefloquine. Portions of the minutes are marked exempt under 5 U.S.C. § 552(b)(5) because the comments made at the meeting by agency participants were non-attribution.

You may seek judicial review of my determination pursuant to 5 U.S.C. § 552(a)(4)(B) in a United States District Court.

If you have any questions on processing your request under the FOIA, please contact Ms. Nadine Brown at the Defense Health Agency Privacy and Civil Liberties Office at (703) 275-6009.

Sincerely,

Paul T. Cygnarowicz
Deputy General Counsel
Defense Health Agency

Enclosure:
As stated

EpiChiefs' Highlights
October 23, 2014

EpiChiefs' is a telephone conference call for Tri-service leaders in epidemiology. It is hosted by AFHSC and held every two weeks. The call provides a forum for the informal exchange of professional information and offers an opportunity for professional consultation and discussion across service lines. The purpose of this summary is to highlight important, current topics that were discussed in order to stimulate further discussion, collaboration, and cooperation.

Participants: AFHSC, AFMES, AFMOA, AFMSA, BUMED, CENTCOM, DHA, DHA-IHCB, EUCOM, HQMC, NCMI, NHRC, NORTHCOM, NMCPHC, PACOM, PHCR-P, PHCR-S, POPM, USAFSAM, USAMMDA, USAMRIID, WRAIR-MRSN, WRAIR-PM, WRAIR-VD

Situational Awareness for CCMDs: B(5) continues to monitor Ebola Virus Disease (EVD) and publishes summaries three times a week (Mon/Wed/Fri). Chikungunya cases continue to be reported; Nicaragua and Montserrat have reported local transmission. Enterovirus D68 is on a downward trend. New MERS-CoV infections continue; a small outbreak in Taif, Saudi Arabia has occurred and one case (imported) was detected in Turkey. Two cases of avian influenza A/H7N9 were reported in China. B(5) noted an NCMI paper about Ebola transmission and that the virus is unlikely to be spread via the airborne route. The 25-bed hospital in Liberia is up and running, and estimated to be seeing patients by early Nov. USPHS will staff the hospital. The CDC is considering lowering its screening temperature for possible EVD cases to a threshold of 100.4°F; however the clinical criterion of 101.5°F is still the official published case definition. B(5) noted that personnel deploying to West Africa should receive malaria prophylaxis with Malarone or doxycycline. B(5) noted that mefloquine is no longer authorized and that it is important that deploying personnel are educated about malaria prevention. B(5) summarized guidance about EVD precautions for those returning from West Africa: no TDY or leave for 21 days; personnel can come to work and be with their families, but may not be in public places or take public transportation. B(5) reported that a 30-person DoD EVD response team (20 nurses, 5 ID docs, 5 trainers) for CONUS is now being assembled, and it has begun 3.5 days of training at Ft. Sam Houston. Also reported was a Marine who visited Guinea in SEP and, upon return to his station (29 Palms), developed high fever; eventually he was diagnosed with *P. falciparum* malaria. He was reportedly prescribed chloroquine for malaria prophylaxis – inappropriate for West Africa. B(5) reported that, in the context of the enterovirus outbreak, 14 bases had submitted 68 specimens; 47 were positive for rhinovirus/enterovirus. Of 18 submitted to CDC for EV testing, and of 13 tested, positive results for EV-D68 were found for 7 from JB Langley-Eustis and 1 from Ft. Drum. Seven patients were hospitalized, aged 2-9 years. The Ali-al-Salem outbreak of ILI in AUG and SEP yielded 15 specimens positive for influenza A/H3. B(5) reported that lab testing at Mayo clinic has found 16 (or 17) positive serologies for leptospirosis among Marines in Okinawa. B(5) noted that labs at Beaumont and Womack Army Medical Centers will be getting the EUA Ebola assay. The five locations that already have testing capability are: USAMRIID, Landstuhl RMC, NAMRU-3(Egypt), NHRC, and NIDL at NMRC.

Respiratory Illnesses: B(5) noted that global influenza activity is low. Some influenza B activity has been reported in Peru. B(5) reported no influenza detected in 173 samples. There was one case of influenza B in an unvaccinated recruit at Paris Island whose specimen was collected on 1 OCT. Testing of older specimens from a Ft. Sill outbreak found a number positive for coxsackie virus (a subtype of enterovirus). B(5) reported for weeks 41/42: of 98 specimens tested, 5 were positive for influenza A/H3 and 3 for influenza B. B(5) reported that among 11 samples received from 3 different embassies, positive results were found for rhino/enteroviruses and other viruses but no influenza. B(5) reported 82% distribution on influenza vaccine shipped as of last week. Compliance is being reported weekly. See http://www.vaccines.mil/

Announcements: B(5) noted the International Conference on Emerging Infectious Diseases will be held during the interval 8-11 MAR 2015 in Atlanta, GA. The deadline for submitting abstracts is 23 OCT 2014.

Next Teleconference: 6 NOV 2014

CONTACT AFHSC:
B(5) B(5) B(5)

EpiChiefs' Highlights
3 May 2018

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Participants: AETC, AFHSB, AFMSA, APHC, Army OTSG-PM, CENTCOM, DHA-IHB, DHA-Vet Svcs, MIDRP, NCMI, NHRC, NMCPHC, PACOM, PHCR-P, USAFA, USAFSAM, USAMMDA-FHP, USCG, WRAIR-VD

Situational Awareness for CCMDs: B(5) reported tracking outbreaks of avian influenza from many locations around the world as well as UN efforts to begin administering cholera vaccine in Yemen in response to the severe outbreak there. B(5) reported on the outbreak of 121 STEC cases (including 1 death) in the U.S. associated with romaine lettuce from Arizona, and the outbreak of 23 cases of salmonellosis linked to eggs. An egg recall was issued because of the latter, but apparently some eggs had been shipped to other countries and territories. B(5) also noted an outbreak of about 4,000 chikungunya cases in Rio de Janeiro State, Brazil, and reports of increased incidence of Buruli ulcer (caused by *Mycobacterium ulcerans*) in an endemic region of Australia. B(5) reported that a small outbreak of salmonellosis among U.S. personnel in Qatar was quickly halted.

Respiratory Disease Updates: B(5) reported 10 (13%) of 76 specimens were positive for influenza over the past 2 weeks. All were influenza type B isolates and they came from civilian residents near the border with Mexico. B(5) also noted that the identification of 5 isolates of influenza A/H3N2 from recruit trainees in March has been followed by finding only 1 influenza isolate in the most recent 44 specimens from trainees. Rates of febrile respiratory illness (FRI) have remained low at all basic training centers B(5) noted that 5 out of 21 respiratory specimens from Ft. Leonard Wood, MO, in the last few weeks have tested positive for *Chlamydia pneumoniae*, a respiratory pathogen that has been identified there in the past. FRI rates remained low there. Also noted was the detection of 14 cases of conjunctivitis caused by *Streptococcus pneumoniae* at Camp Pendleton. B(5) reported processing 212 specimens from weeks 16 and 17. Percentages of specimens positive for influenza in each week were 24% and 13%, respectively. During the two week period, the numbers of influenza isolates by type were 10 A/H3, 7 A/H1N1, and 25 B. B(5) reported that Army laboratories had identified respiratory pathogens in 6% of specimens, among which the distribution of pathogens was 32% influenza A and 51% influenza B. For the total influenza season, there have been 209 influenza-associated hospitalizations reported through DRSi (including 31 among active duty soldiers). At this time last year, there had been only 92 such hospitalizations. B(5) reported that the rates of influenza-like illness in the combatant commands in week 17 were generally described as minimal, except for low rates in 5 states and Korea. B(5) reported that the cluster of probable cases of mumps among 4 civilian workers at the Coast Guard Yard in Baltimore has been followed by no additional cases in over a month.

Gastrointestinal Disease Updates: B(5) reported that rates of acute gastroenteritis have been low at the basic training centers and no pathogens have been isolated in the last 2 weeks.

Other: B(5) reported an ongoing investigation into a possible link between the use of smallpox vaccine among service members and possible cases of myocarditis and pericarditis. B(5) noted local TV news reports in Washington about the military's use of mefloquine for malaria prophylaxis and the possible short- and long-term side effects.

Next Teleconference: 17 MAY 2018

CONTACT AFHSB:
B(5) B(5) B(5)

EpiChiefs' Highlights
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Announcements: B(5) noted the International Conference on Emerging Infectious Diseases will be held during the interval 8-11 MAR 2015 in Atlanta, GA. The deadline for submitting abstracts is 23 OCT 2014.

Next Teleconference: 6 NOV 2014

CONTACT AFHSC:
B(5) B(5) B(5)

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JUL 25 2018

Dr. Remington Nevin
MuckRock
DEPT MR 22301
PO Box 55819
Boston, MA 02205-5819

Re: Freedom of Information Act (FOIA) Appeal 2016-064

Dear Dr. Nevin:

On November 9, 2015, you requested under the Freedom of Information Act (FOIA), the Defense Health Agency (DHA or "agency") provide: "An unredacted copy of the undated presentation titled "Neuropsychiatric Adverse Events Following Mefloquine Exposure," authored by the Senior Managing Epidemiologist, division of Epidemiology & Analysis, Armed Forces Health Surveillance Center (AFHSC), which was sent by email from the official account of Dr. Eick-Cost of AFHSC on August 1, 2014 [. . .]"

On April 20, 2016, the DHA FOIA office provided a redacted copy of the requested information, citing 5 U.S.C. § 552(b)(5), which exempts internal records that are deliberative in nature and part of the decision-making process, containing opinions and recommendations.

You filed an appeal to FOIA 2016-064 on April 24, 2016. The appeal is granted in part. Upon review, the AFHSC provided the requested presentation, maintaining some of the recorded data, as compiled in the presentation, is still subject to exemption 5 U.S.C. § 552(b)(5). Redacting this intra-agency record prevents deceiving the public with inaccurate or misleading information. The Armed Forces Health Surveillance Center explained the presentation facilitated a peer reviewed article which is attached to the response.

You may seek judicial review of this determination pursuant to 5 U.S.C. § 552(a)(4)(B) in a United States District Court.

If you have any questions on processing your request under the FOIA, please contact Ms. Nadine Brown at the Defense Health Agency Privacy and Civil Liberties at (703) 275-6009.

Sincerely,

Paul T. Cygnarowicz
Deputy General Counsel
Defense Health Agency

Enclosure:
As stated

Neuropsychiatric Adverse Events following Mefloquine Exposure

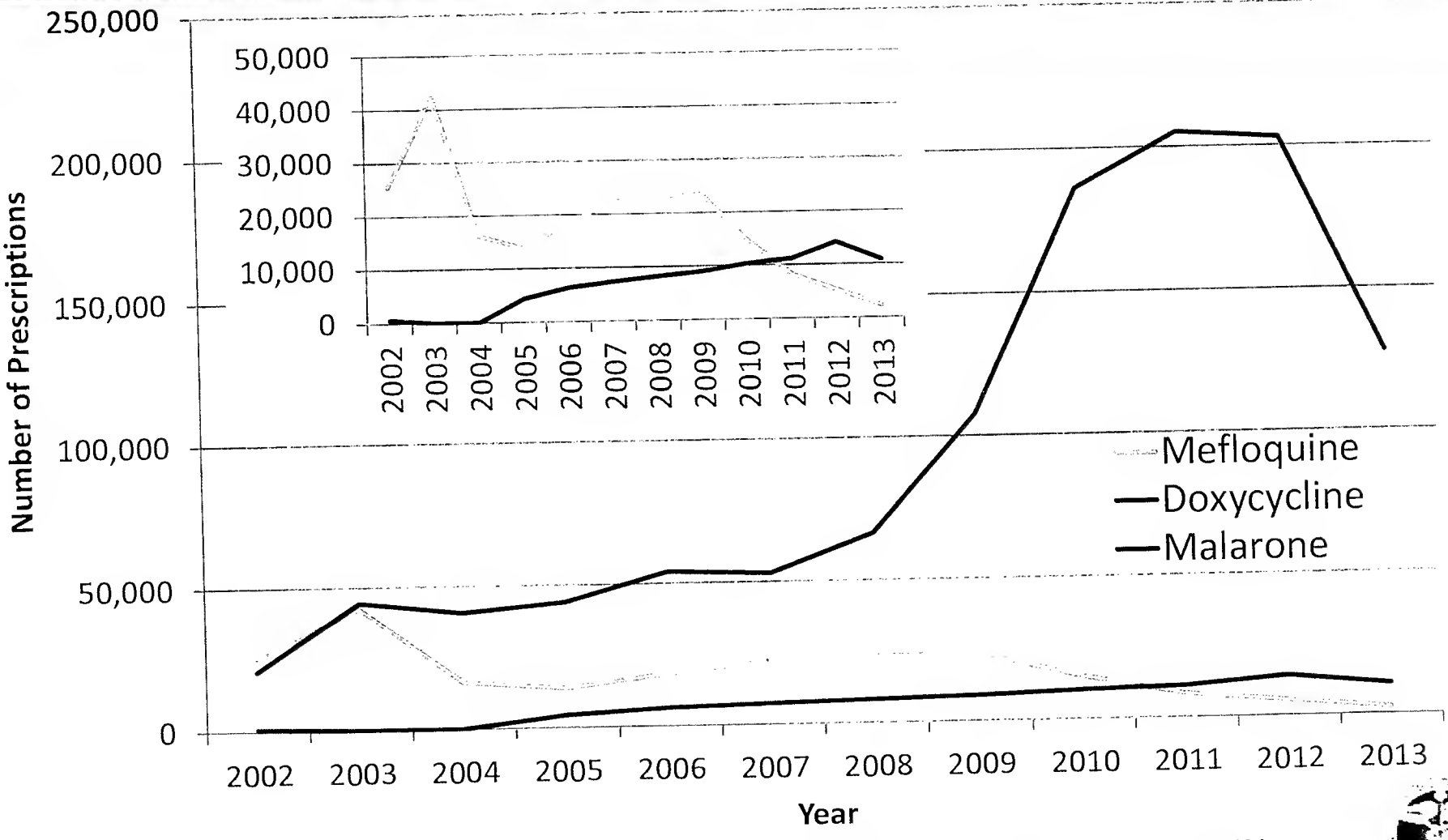
B(5)
B(5)

Division of Epidemiology & Analysis
Armed Forces Health Surveillance Center

Outline

- Anti-malarial prescription use
- Study objectives
- Population descriptions
- Study methods
- Results
- Summary of findings

Anti-Malarial Prescription Use: 2002-2013



*Theater prescriptions included from 2008 -2013; 2013 data through 30 JUN

Study Objectives

- Assess risk of neuropsychiatric adverse events following mefloquine exposure compared to doxycycline or atovaquone/proguanil exposure
- Determine the prevalence of neuropsychiatric diagnoses prior to prescriptions and compare the occurrence of the outcomes following prescriptions between those with and without prior history of neuropsychiatric events
- Describe the proportion of cases who continue to have persistent medical encounters up to 24 months following incident diagnosis

Study Populations

- Active component service members
- Anti-malarial prescription (PEC and TMDS data): 01JAN2008 – 30JUN2013
  - Mefloquine (250mg) (MEF)
  - Doxycycline (100mg, tabular form, daily dose, 30 days or longer prescription) (DOXY)
  - Atovaquone/proguanil (Malarone®) (MAL)
- DOXY and MAL prescriptions excluded if MEF ever prescribed previously or concurrently

Risk windows for outcome of interest

- Risk window definition
  - Entire length of prescription plus 365 days
  - Overlapping prescriptions merged to extend risk window
- Multiple risk windows allowed per individual
  - Looked at one dose only, but no remarkable difference in results – data will not be shown
- Risk window censoring
  - MEF prescription censored at time of DOXY or MAL if prescribed during same risk window
  - Censored at outcome of interest, left active component, left military service

Outcomes of interest

- Lifetime incidence rule for outcomes (Obj 1 & 3)
- Data sources: INPT, OUTPT, and TMDS
- Psychiatric Outcomes (DX1/2 only; 1 INPT, 2 OUTPT/TMDS within 180 days of each other, or 1 OUTPT at mental health clinic)
  - Anxiety disorders
  - Depressive disorders
  - Adjustment disorders
  - PTSD
  - Psychoses

Outcomes of interest

- Neurologic outcomes (1 encounter; any DX position)
  - Tinnitus
  - Vertigo
  - Convulsions
- Other outcomes
  - Insomnia (any DX, 1 INPT or 2 OUTPT/TMDS w/in 90 days)
  - Suicide ideation (1 encounter, any DX)
  - Completed suicide (casualty data, manner = suicide)

Objective 1:

Assess risk of neuropsychiatric adverse events following MEF exposure compared to DOXY or MAL exposure

Population Characteristics

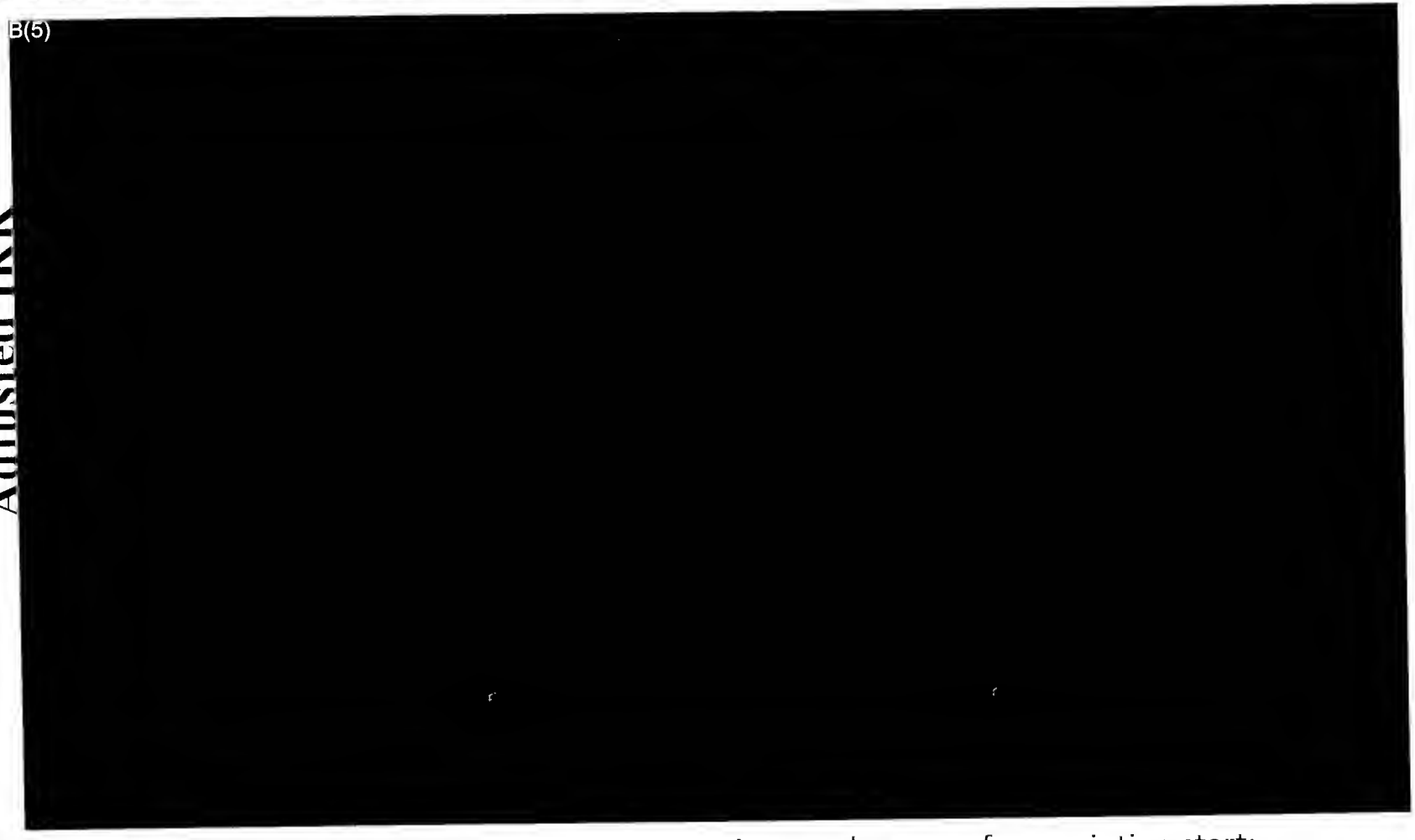
		MEF		DOXY		MAL	
		N	%	N	%	N	%
		36,538	100	318,421	100	12,881	100
Age	17-19	B(5)					
	20-29						
	30-39						
	40+						
Service	Army						
	Navy						
	Air Force						
	Marine Corps						
	Coast Guard						
Grade	E1-E4						
	E5-E9						
	O1-O3/W01-3						
	O4-O9/W4-5						

Prescription and Deployment Characteristics

		MEF		DOXY		MAL	
		N	%	N	%	N	%
		36,538	100	318,421	100	12,881	100
Year of Prescription	2008	B(5)					
	2009						
	2010						
	2011						
	2012						
	2013						
Deployed during risk window	N						
	Y						
Combat Exposed	N						
	Y						
	Missing						
	NA						

Tinnitus
(ICD-9: 388.3)

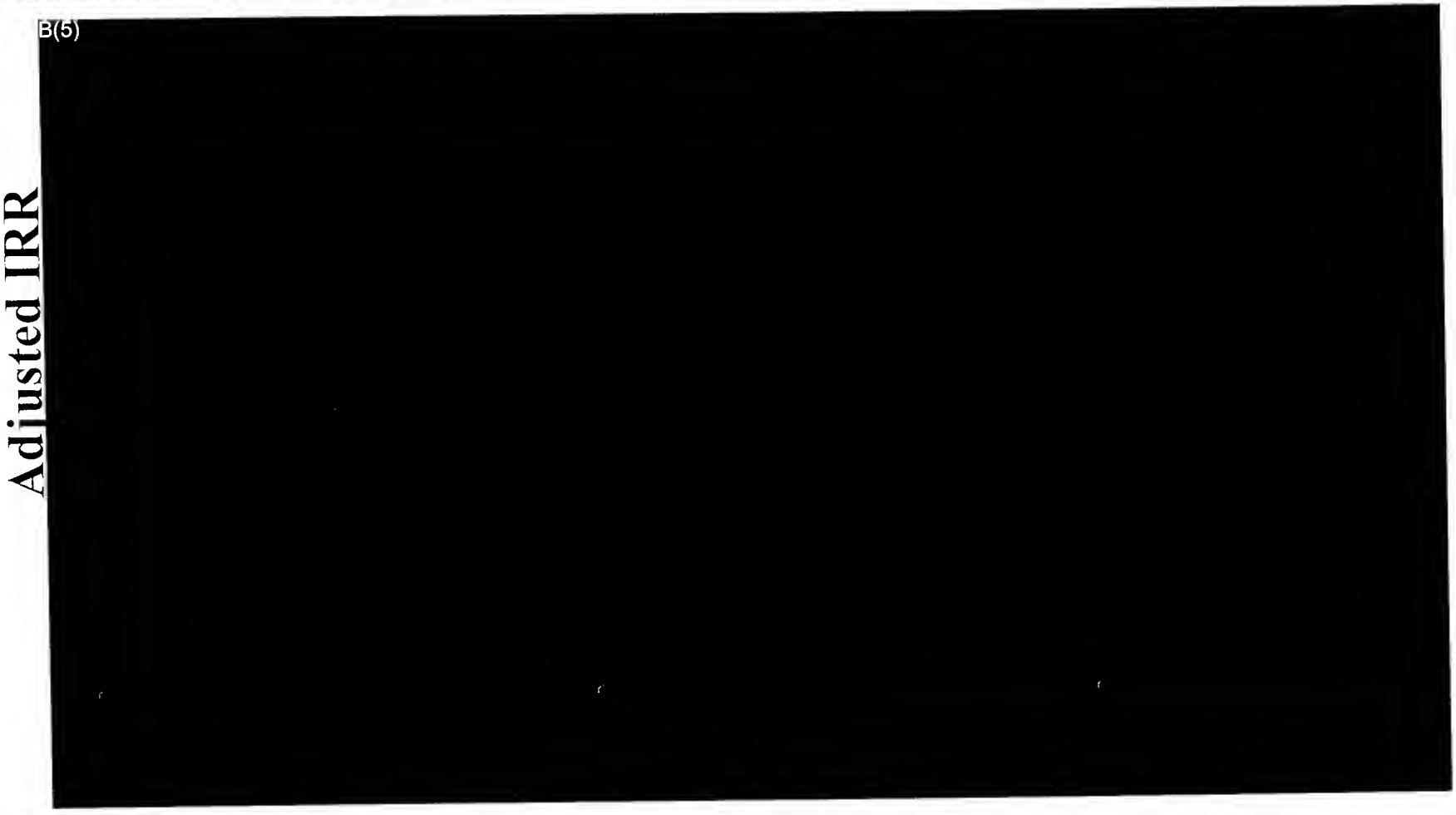
B(5)



Bars indicate 95% CI; Adjusted for age, sex, service, grade, year of prescription start; Deployed also adjusted for location and combat exposure

Vertigo
(ICD-9: 386.1, 386.2)

B(5)



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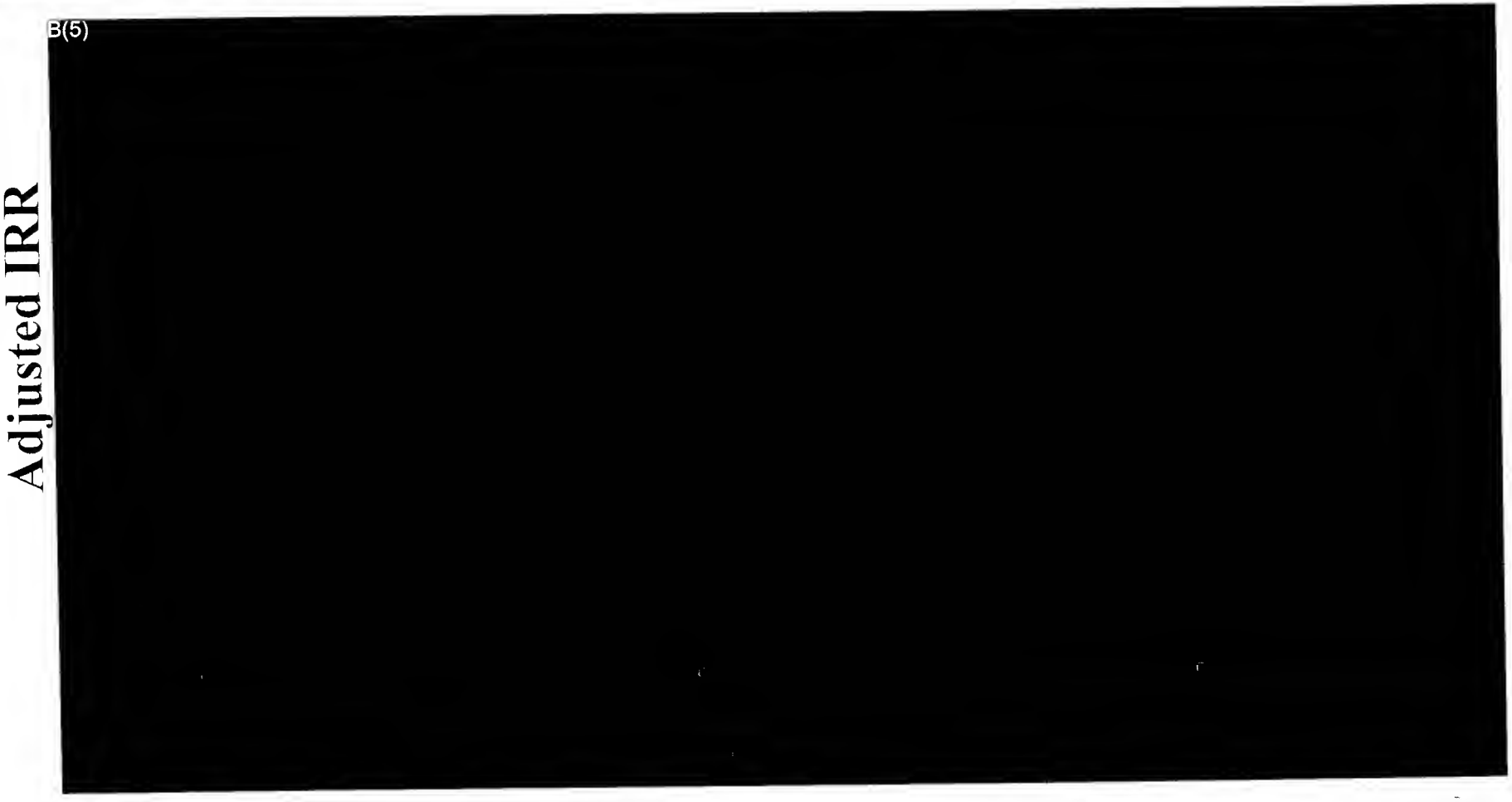
Convulsions
(ICD-9: 780.3 exact , 780.39)

B(5)



Bars indicate 95% CI; Adjusted for age, sex, service, grade, year of prescription start; Deployed also adjusted for location and combat exposure

Anxiety
(ICD-9: 300.0x, 300.2x 300.3x)

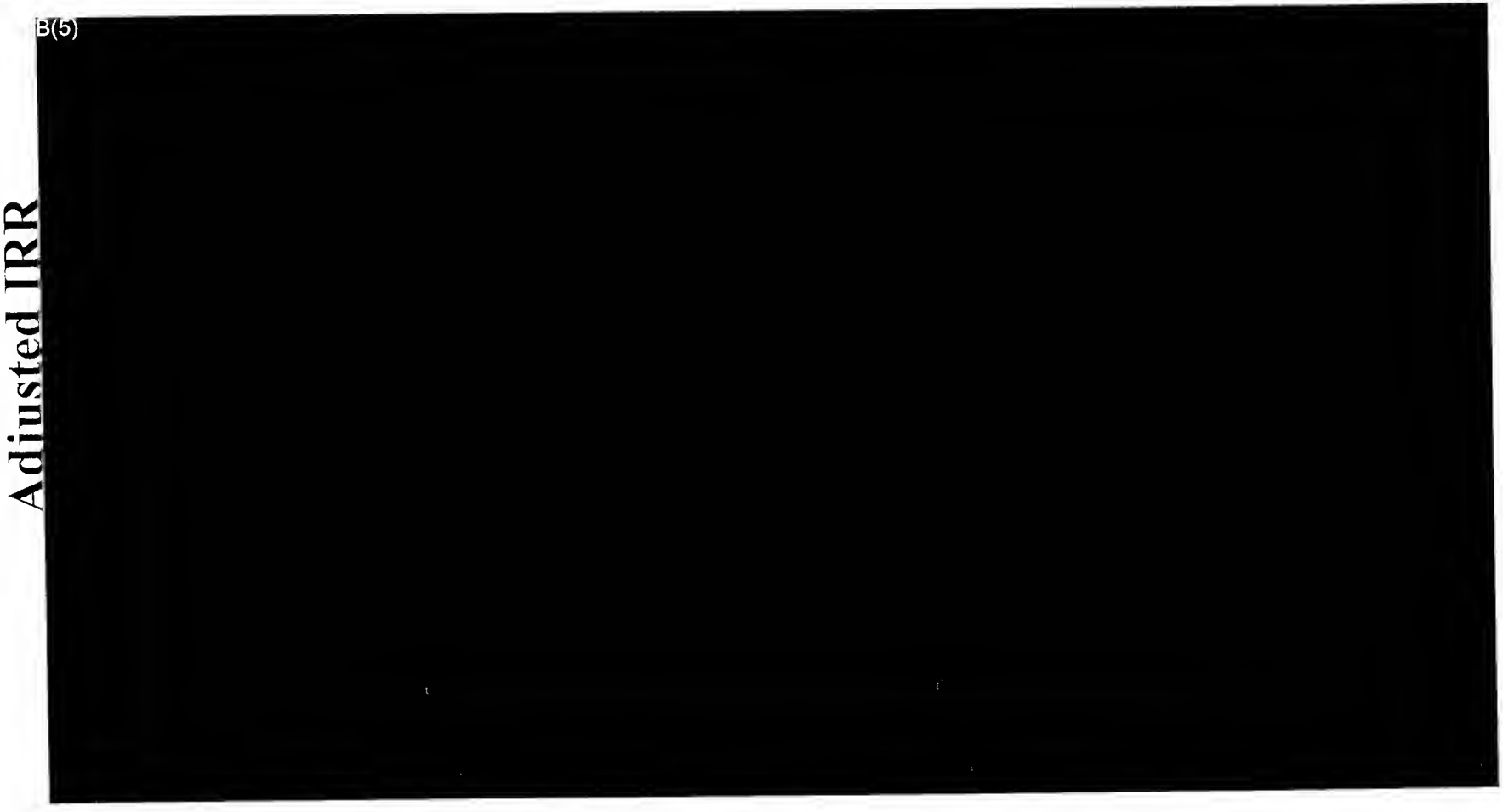
B(5)

Adjusted IRR

Bars indicate 95% CI; Adjusted for age, sex, service, grade, year of prescription start; Deployed also adjusted for location and combat exposure

Depressive disorders
(ICD-9: 296.2x, 296.3x, 296.9, 296.90, 296.99, 311.xx)

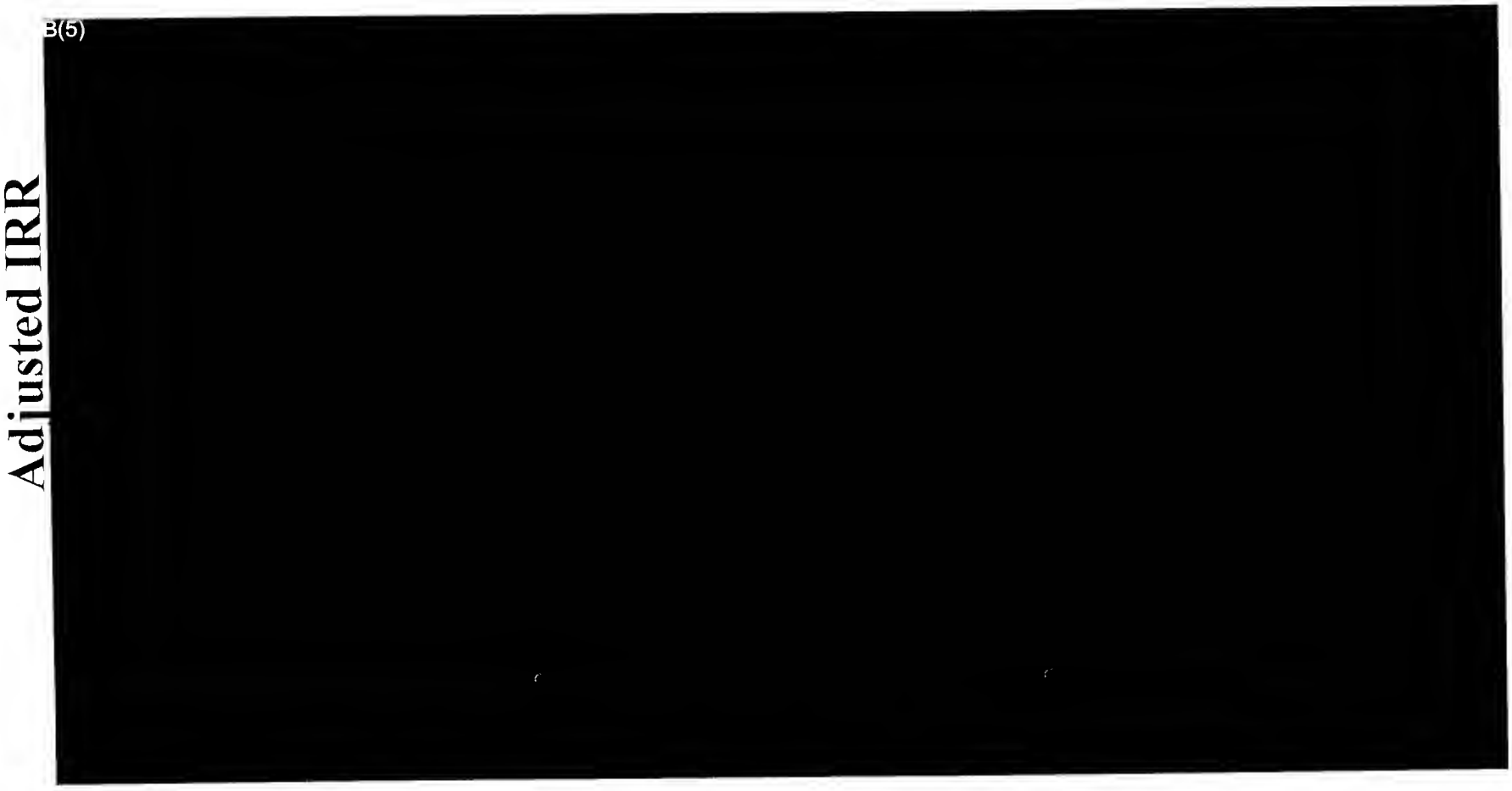
B(5)



Bars indicate 95% CI; Adjusted for age, sex, service, grade, year of prescription start;
Deployed also adjusted for location and combat exposure

Adjustment disorders
(ICD-9: 309.xx (excluding PTSD, 309.81))

B(5)



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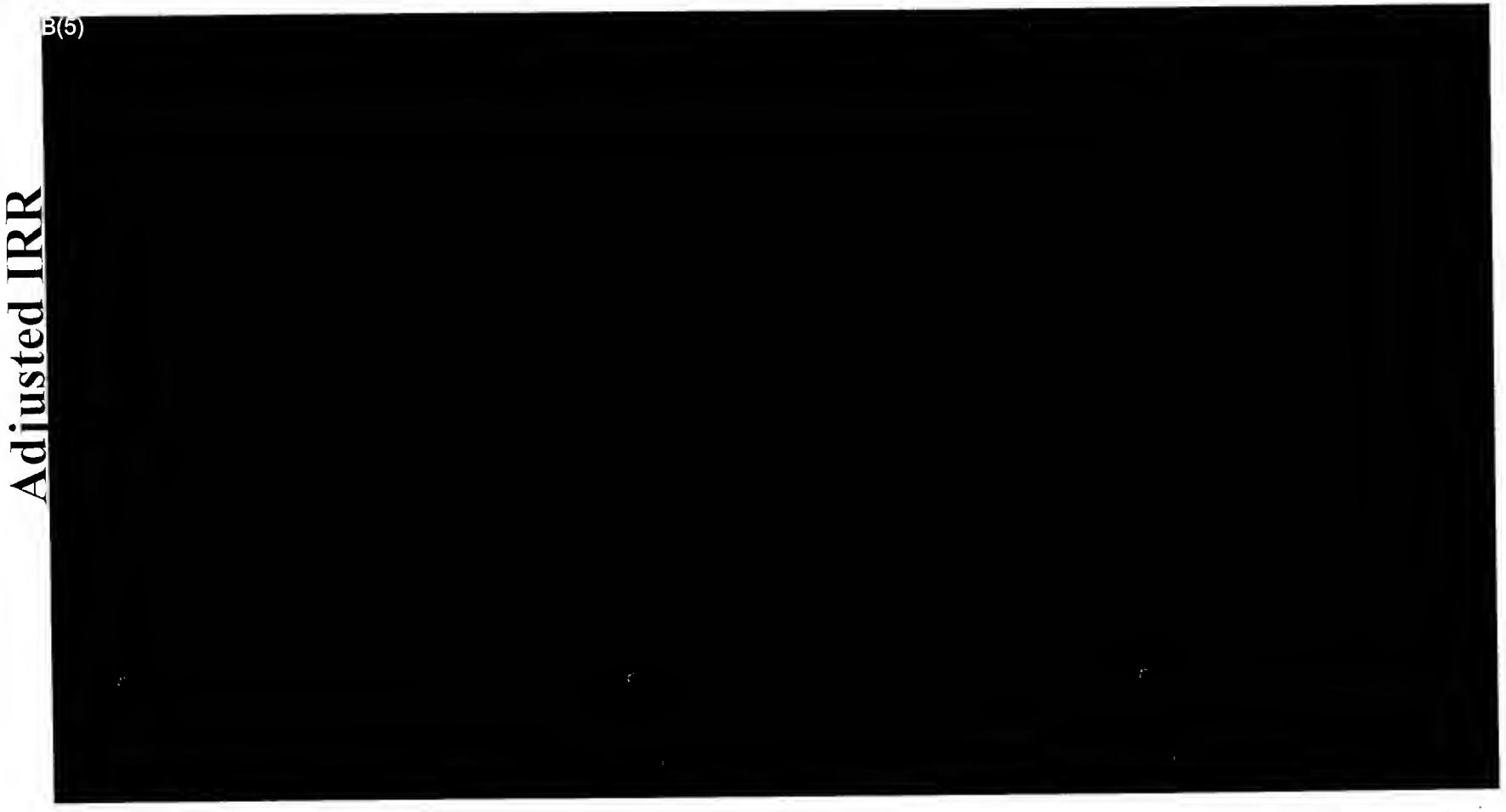
PTSD
(ICD-9: 309.81)

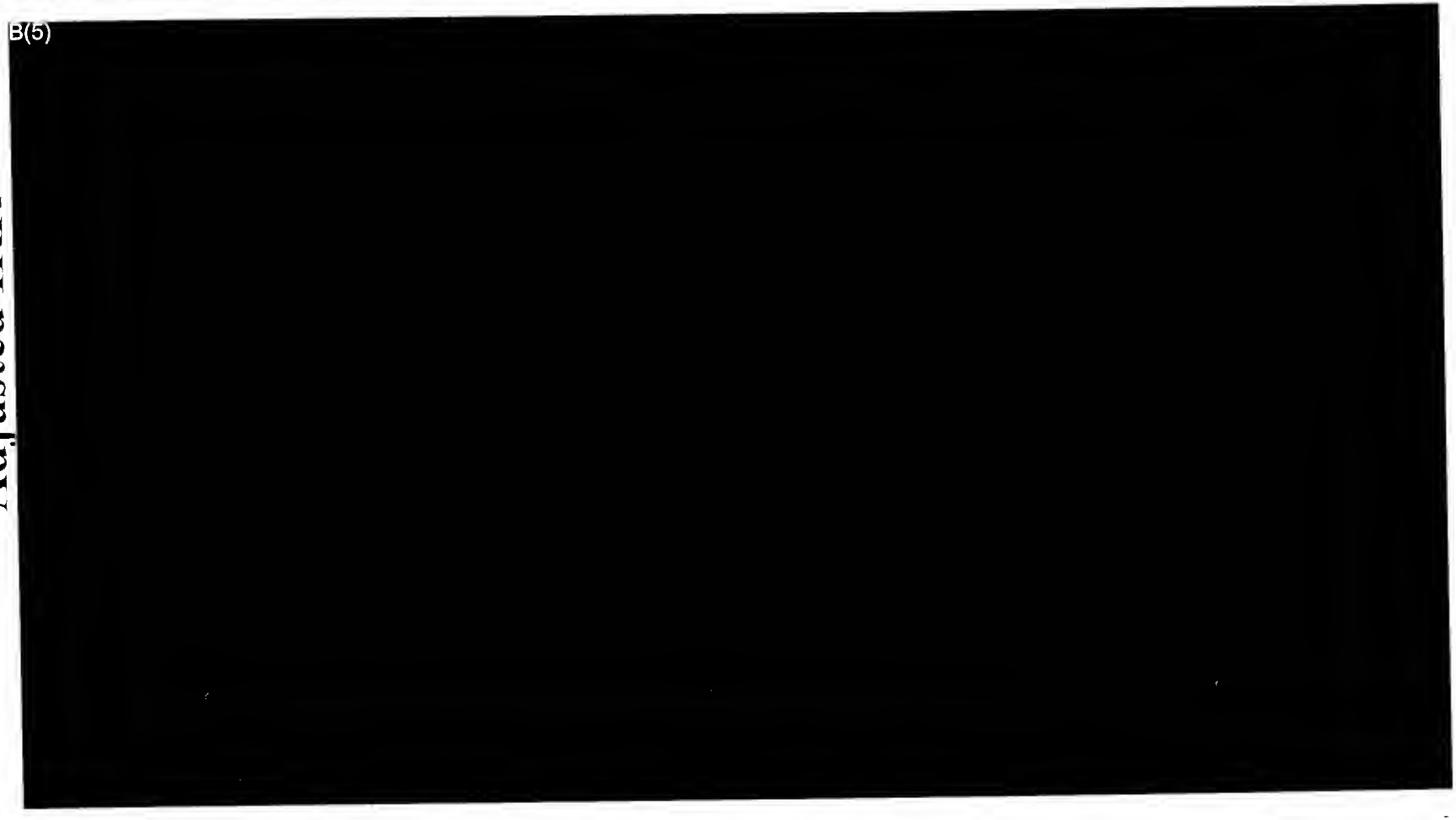
B(5)



Bars indicate 95% CI; Adjusted for age, sex, service, grade, year of prescription start; Deployed also adjusted for location and combat exposure

Psychosis
(ICD-9: 297.xx, 298.xx, 293.81, 293.82)

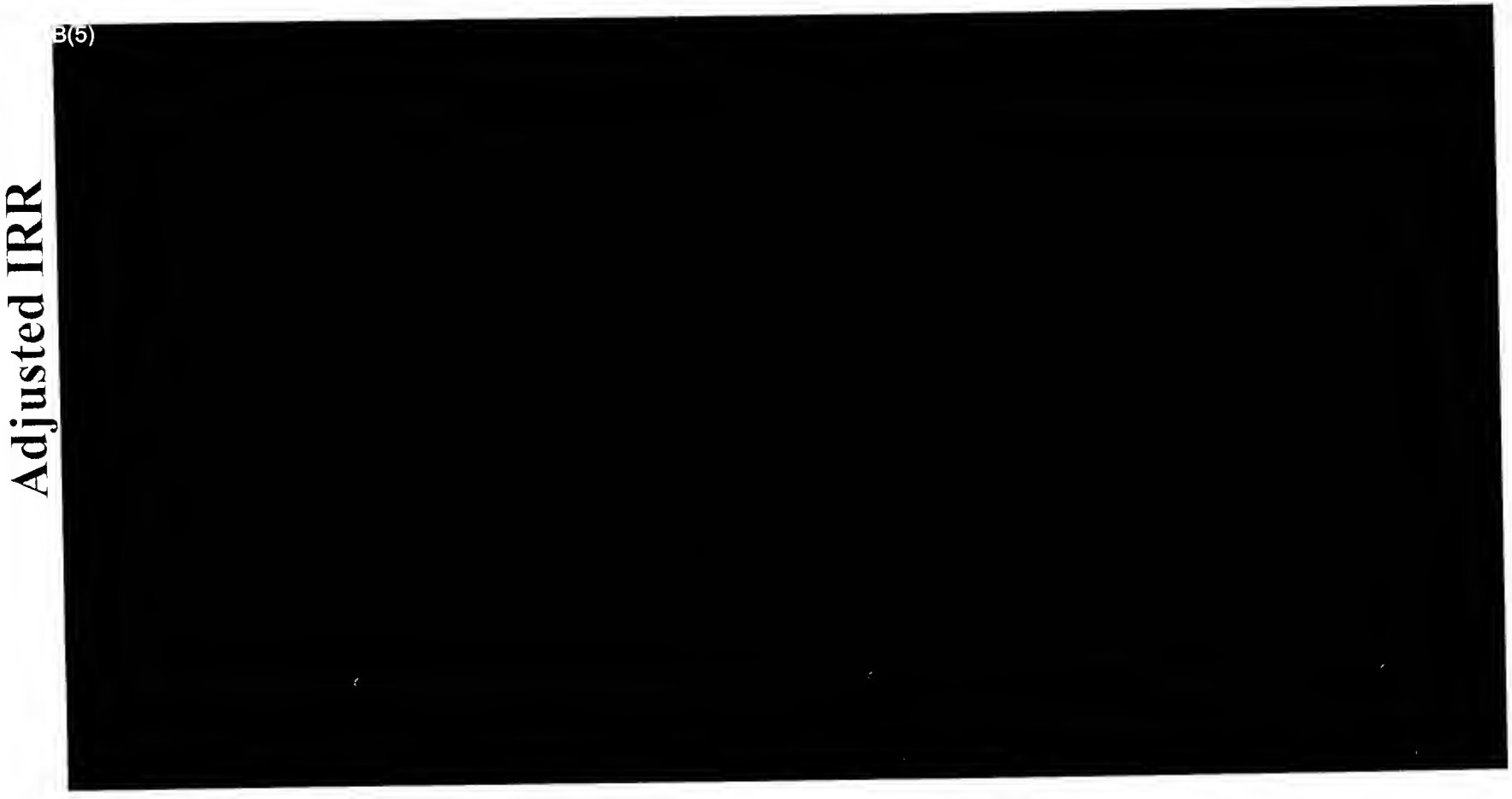
B(5)



Bars indicate 95% CI; Adjusted for age, sex, service, grade, year of prescription start; Deployed also adjusted for location and combat exposure

Insomnia
(ICD-9: 307.41, 307.42, 327.00, 327.01, 372.02, 327.09, 780.52)

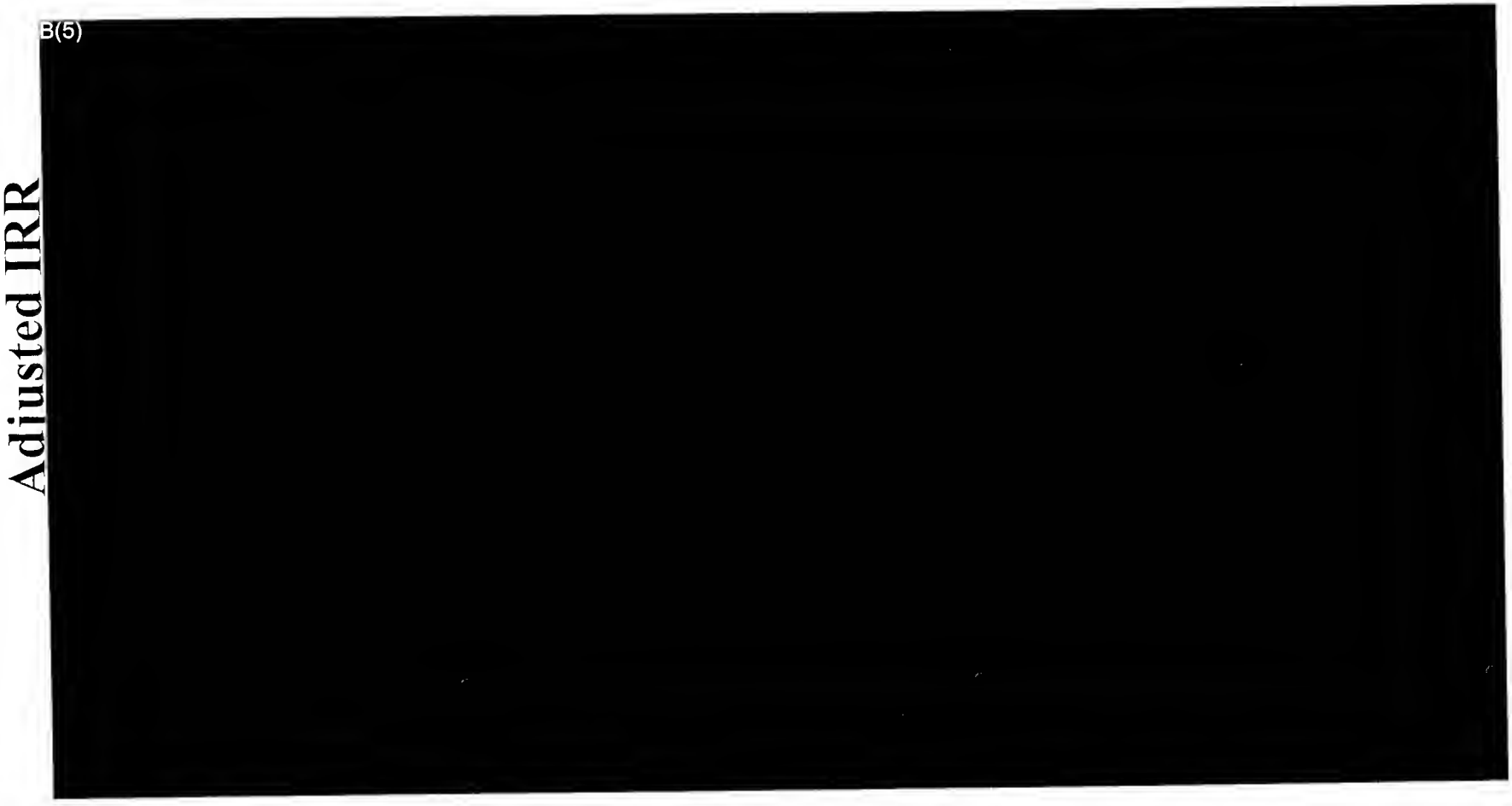
B(5)



Bars indicate 95% CI; Adjusted for age, sex, service, grade, year of prescription start;
Deployed also adjusted for location and combat exposure

Suicide Ideation
(ICD-9: V62.84)

B(5)



Bars indicate 95% CI; Adjusted for age, sex, service, grade, year of prescription start; Deployed also adjusted for location and combat exposure

Suicide

B(5)

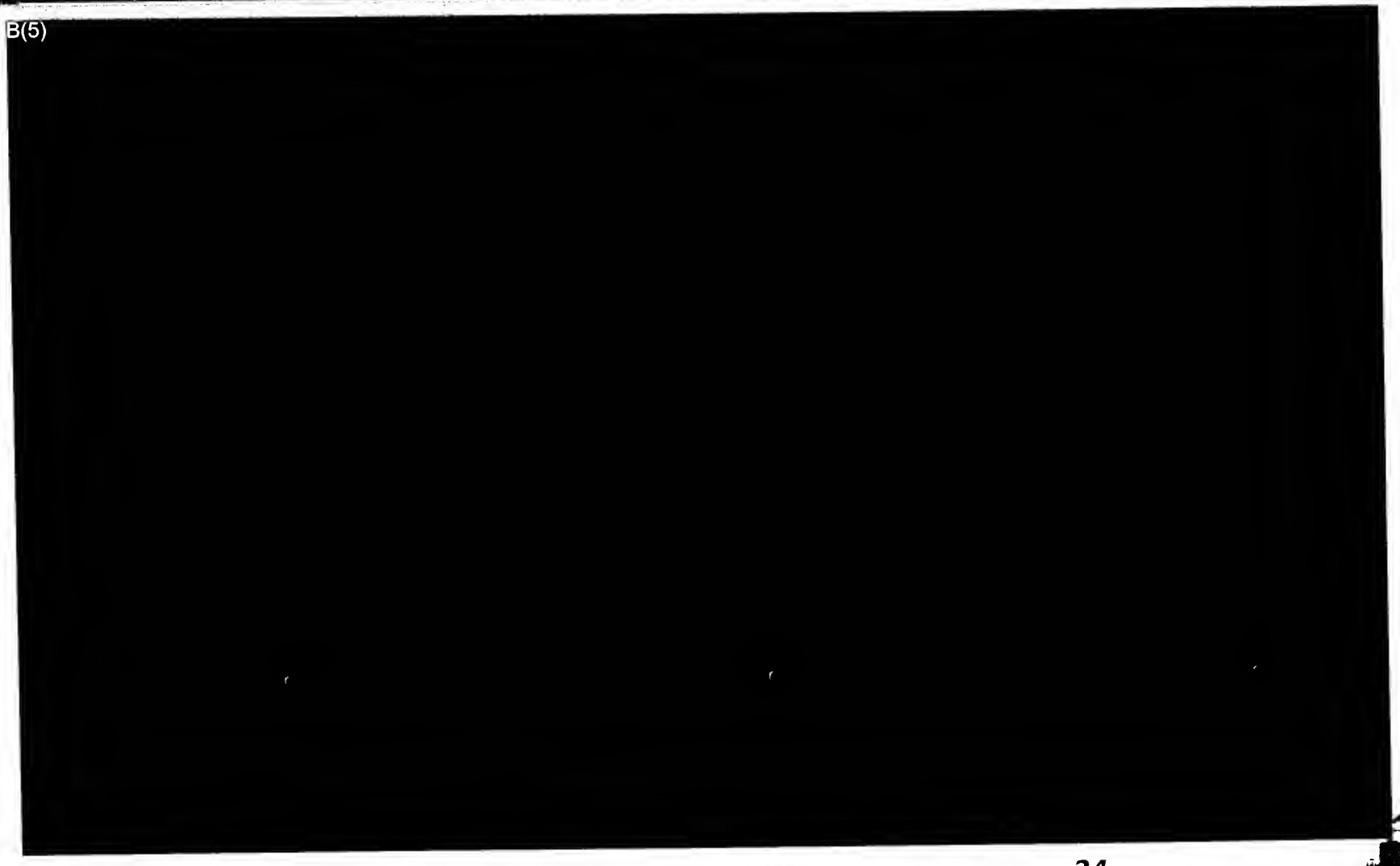
[redacted]

Objective 2:
Subjects are allowed to have history of outcomes

(2a) Determine the percentage of subjects who received a prescription, but who had a neuropsychiatric diagnosis in the 1 year prior (contraindication for MEF)

Percentage of subjects with a neuropsychiatric diagnosis in the 1 year prior to prescription

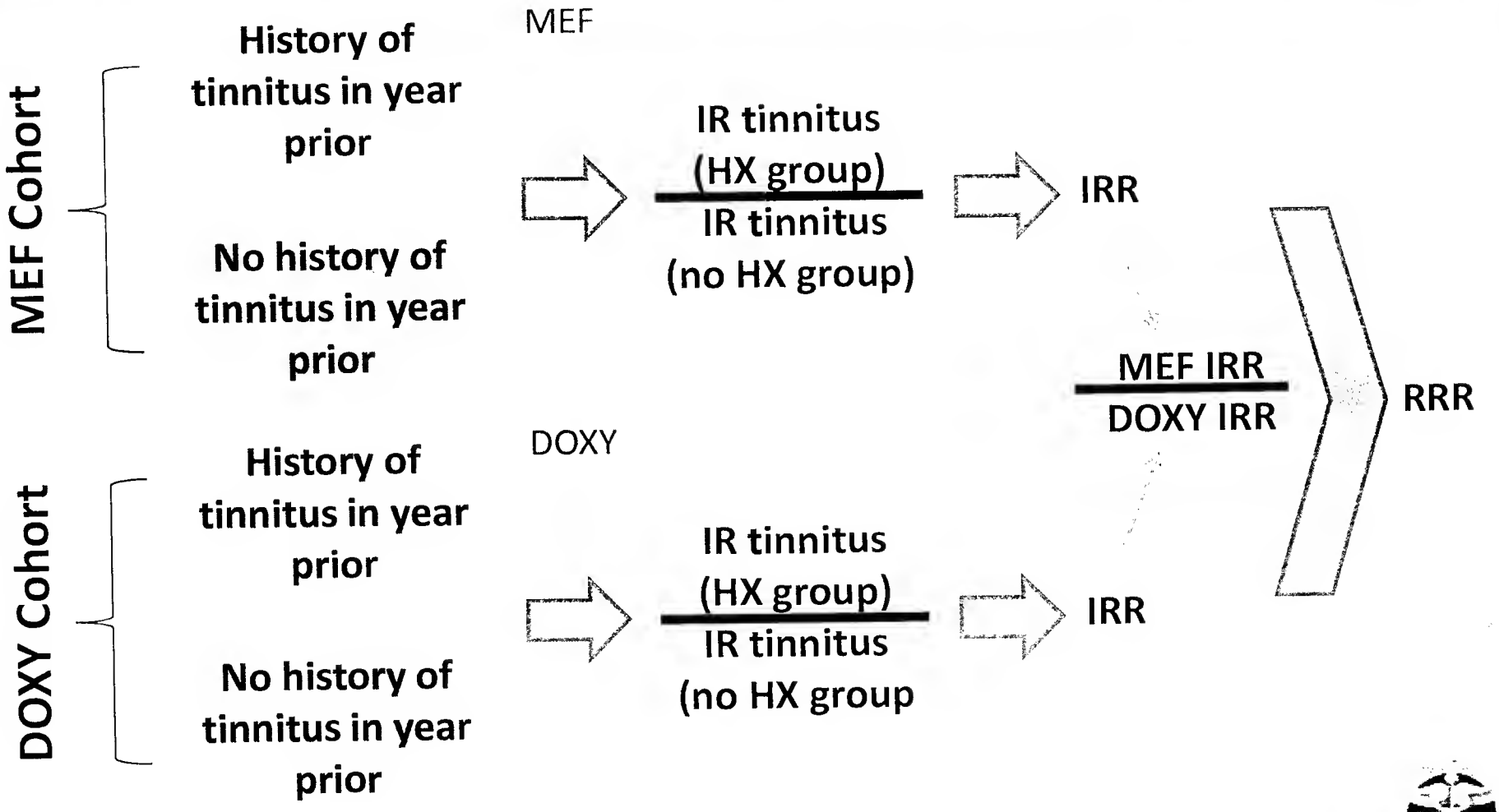
B(5)



Objective 2:
Subjects are allowed to have history of outcomes

(2b) Is the risk of neuropsychiatric outcomes following prescription different for individuals with and without a prior history and is this difference comparable between MEF and DOXY

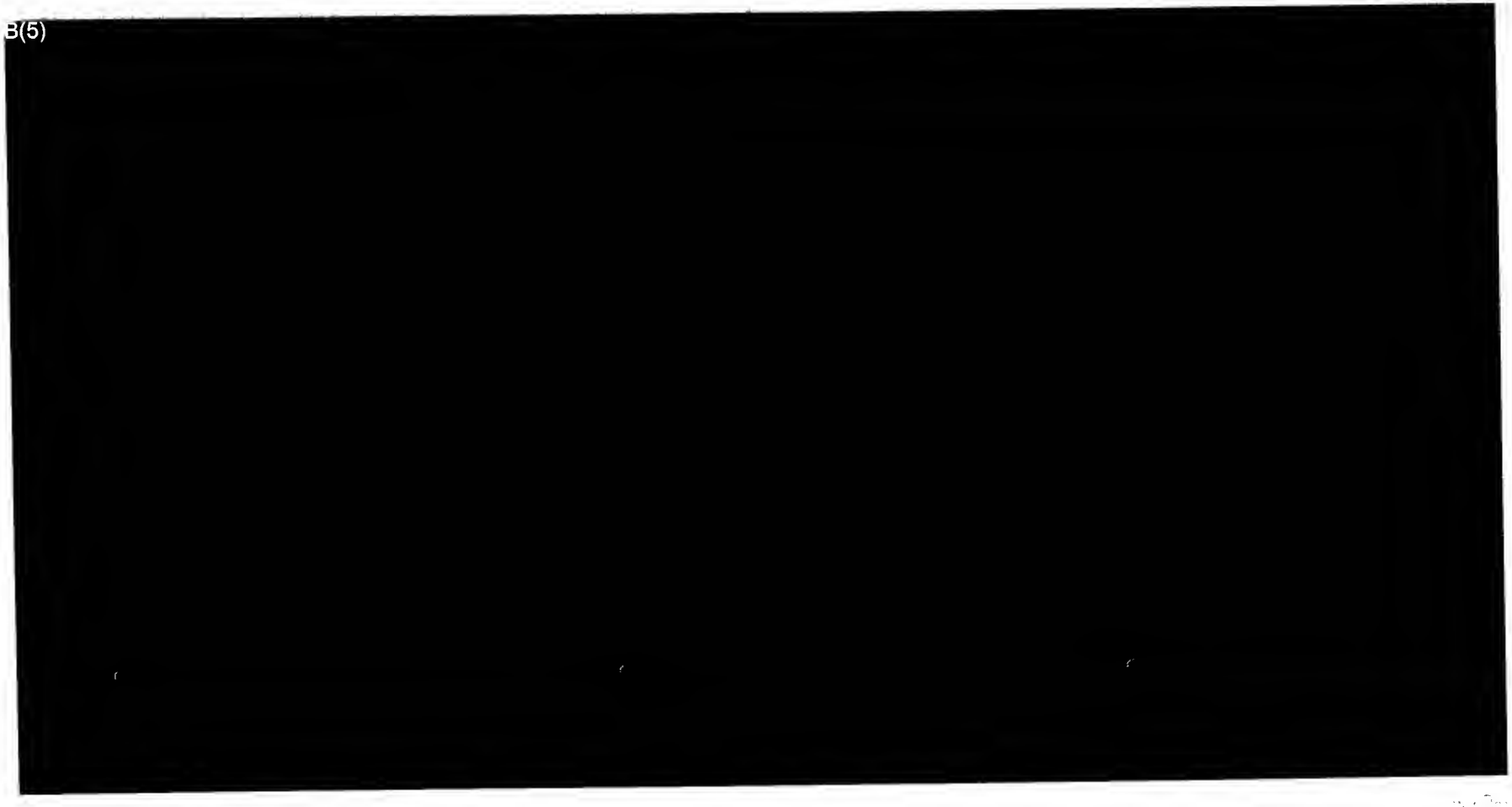
Objective 2b Methods (Tinnitus example)



IR = Incidence rate; IRR = Incidence rate ratio; RRR = Ratio of the incident rate ratios

Risk comparison between individuals with and without a 1 year prior history by cohort ; and MEF vs. DOXY RRR estimates

B(5)



[a]Adjusted for age, sex, service, grade, current deployment, year of prescription start

Ratio of Incidence Rate Ratio (RRR)

1. Permutation test:
   - Underlying distribution of RRR unknown, parametric approach not applicable.
   - Assume null hypothesis is true (RRR=1)
   - Shuffle exposed and unexposed data to simulate the distribution under null hypothesis.
   - How extreme is the observed RRR? The rank of this observed RRR gives p-value.
   - Computationally intensive, Monte Carlo simulate ran 2000 times (1000 times run gives uncertainty +/-1% near p=0.05).
   - P-values were computed using the exact test procedure by fixing (conditionally) the marginal totals, total number of exposed cases and follow-up time ratios in each stratum additionally, which is computed by enumerating all permutations, i.e the permutation test.
2. Confidence intervals are calculated by Bootstrap resampling with same sample size as the original data set.

Objective 3:

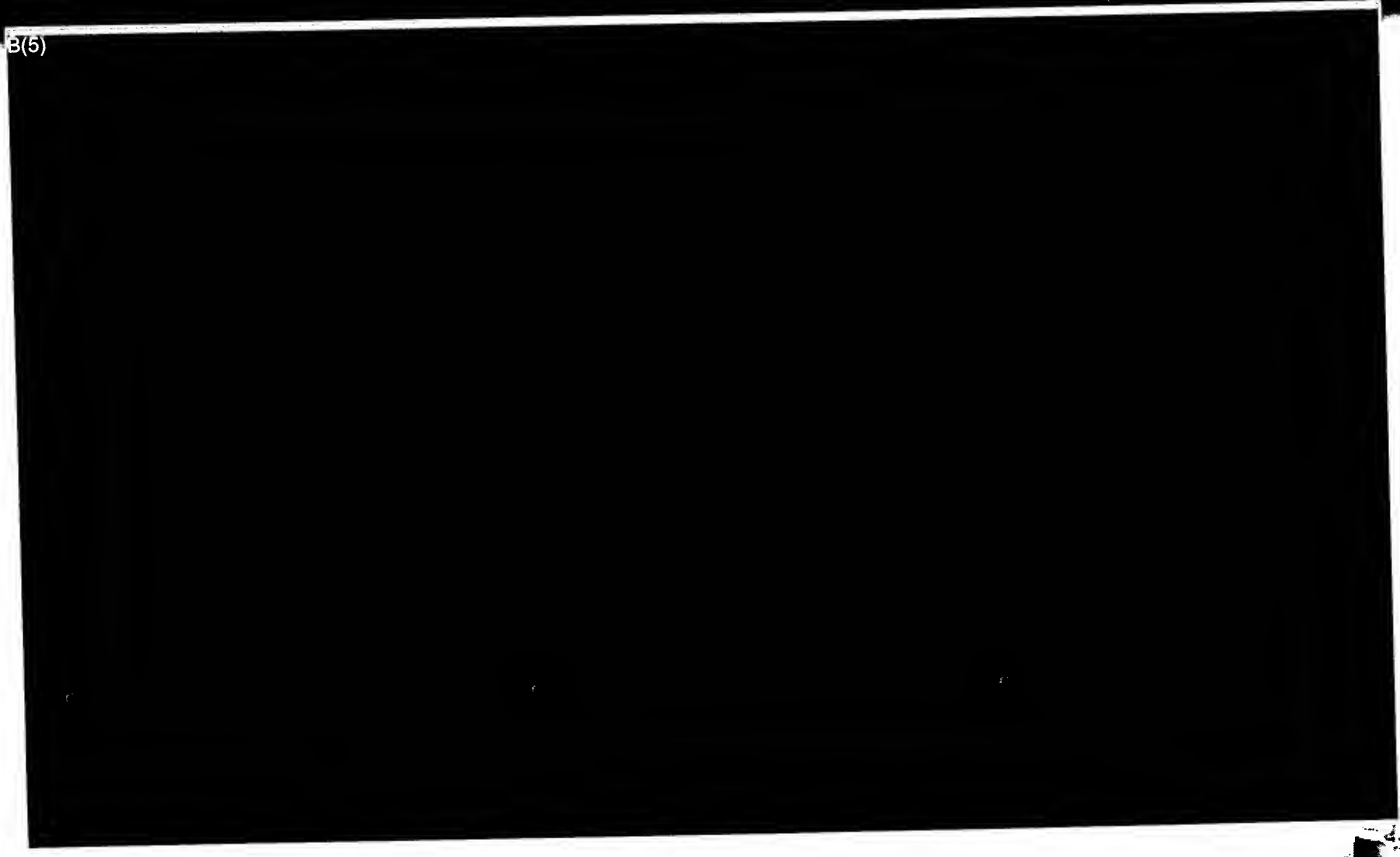
Determine the percentage of cases who continue to have persistent medical encounters up to 24 months following incident diagnosis

Methodology

- Inclusion criteria:
  - Had the outcome of interesting following prescription
  - Stayed in the active component military for at least 24 months following incident diagnosis
- Calculated the percentage of individuals who had an additional medical encounter for the outcome of interest
  - 6 months after incident diagnosis
  - 12 months after incident diagnosis
  - 18 months after incident diagnosis
  - 24 months after incident diagnosis

Persistence of outcomes: MEF compared to DOXY

B(5)



Limitations

- No data on whether individuals took prescribed medication
- Population level analysis - doesn't necessarily mean individuals may not experience these adverse events following MEF
- Administrative data sources
- Minor adverse events that are not medically attended will not be captured

Strengths

- Use of comprehensive electronic medical records
- Inclusion of theater prescriptions and medical encounters
- Large population size and robust statistical methods
- Timely assessment from initiation to completion of analysis

Overall findings

- B(5)

Next Steps

- Summarize findings in peer-reviewed publication
- Any additional analyses requested?

Thank you

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Neuropsychiatric Outcomes after Mefloquine Exposure among U.S. Military Service Members

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Abstract. Mefloquine was widely prescribed to U.S. military service members until 2009 when use was limited to personnel with contraindications to doxycycline and no contraindications to mefloquine. The need to estimate the occurrence of neuropsychiatric outcomes (NPOs) in service members prescribed mefloquine warranted a comprehensive evaluation of this issue. Active component service members filling a prescription for mefloquine, doxycycline, or atovaquone/proguanil (A/P) between January 1, 2008 and June 30, 2013, were included in the analysis. The risk of developing incident NPOs and the risk of subsequent NPOs among subjects with a history of the condition were assessed. A total of 367,840 individuals were evaluated (36,538 received mefloquine, 318,421 received doxycycline, and 12,881 received A/P). Among deployed individuals prescribed mefloquine, an increased risk of incident anxiety was seen when compared with doxycycline recipients (incidence rate ratio [IRR] = 1.12 [1.01–1.24]). Among nondeployed mefloquine recipients, an increased risk of posttraumatic stress disorder (PTSD) was seen when compared with A/P recipients (IRR = 1.83 [1.07–3.14]). An increased risk of tinnitus was seen for both deployed and nondeployed mefloquine recipients compared with A/P recipients (IRR = 1.81 [1.18–2.79]), 1.51 (1.13–2.03), respectively). Six percent of the mefloquine cohort had an NPO in the year before receiving mefloquine. When comparing individuals with a prior neuropsychiatric history to those without, the ratio of relative risks for adjustment disorder, anxiety, insomnia, and PTSD were higher (not statistically significant) for mefloquine compared with doxycycline. These findings emphasize the continued need for physicians prescribing mefloquine to conduct contraindication screening.

INTRODUCTION

Mefloquine was developed by the Walter Reed Army Institute of Research as part of its malaria drug discovery program which began in the 1960s in response to the significant impact of malaria on U.S. troops during the Vietnam War.[1] Mefloquine was approved for use in the United States in 1989. Since that time, numerous contraindications and enhanced warnings have been added to the drug label, including a boxed warning in 2013.[2]

Initially, the military used mefloquine as a first-line drug for the prevention of *Plasmodium* species of malaria. After the 2009 drug label warnings, the Department of Defense (DoD) issued a new policy memorandum (HA Policy 09-017) restricting use of mefloquine to personnel with contraindications to doxycycline and no contraindications to mefloquine.[3] This policy made doxycycline the drug of choice to prevent malaria in deployed military in all areas other than sub-Saharan Africa. Subsequent evolution of this policy resulted in the current 2013 policy which recommends either doxycycline or atovaquone/proguanil (A/P) as first-line medications.[4]

Serious adverse events after mefloquine use are rare.[5–7] Studies evaluating the occurrence of neuropsychiatric outcomes (NPOs) after mefloquine use report mixed results, but a large proportion of these studies found an association between mefloquine and NPOs.[7–17] Due to the extensive use of mefloquine for malaria prevention among service members before 2009 and its continued, limited use, after that point, the need to evaluate adverse events in service members who took the drug is evident. Therefore, a retrospective population-based cohort study was conducted among service members. The primary objective of the study was to assess and compare the risk of NPOs after mefloquine, doxycycline, and A/P prescriptions. The secondary objective was to determine the percentage of the mefloquine and doxycycline cohorts with a neuropsychiatric diagnosis (NPD) in the year before receiving the antimalarial medication and to compare the risk of an NPO following that prescription among subjects with and without a history of an NPD in the year prior and to determine whether this difference in risk is higher among the mefloquine cohort compared with the doxycycline cohort.

MATERIALS AND METHODS

Data sources. Data from the Defense Medical Surveillance System (DMSS), the Pharmacy Data Transaction Service (PDTS), and the Theater Medical Data Store (TMDS) were used for this study. DMSS is the central repository of medical surveillance data for the U.S. Armed Forces and is maintained by the Armed Forces Health Surveillance Branch.[18] DMSS contains longitudinal data on medical encounters (in both military treatment facilities [MTFs] and civilian facilities if paid for by the Military Health System), demographics, service, deployment, and immunizations for service members. TMDS contains medical encounter and pharmacy data from deployed locations. PDTS contains DoD beneficiary prescription data from MTFs, retail pharmacy networks, and mail orders, and was provided by the DoD Pharmacoeconomic Center.

Study population and design. PDTS and TMDS were used to identify the cohort of active component service members who filled a prescription for mefloquine (250 mg), doxycycline (100 mg, tabular form, daily dose, 30-day minimum prescription), or A/P at any time between January 1, 2008 to June 30, 2013. Doxycycline and A/P prescriptions were excluded if the service member previously or concurrently received mefloquine. Doxycycline prescriptions were restricted to the dosage and regimen delineated above in an effort to identify only prescriptions for malaria prophylaxis. Because TMDS is known to have less

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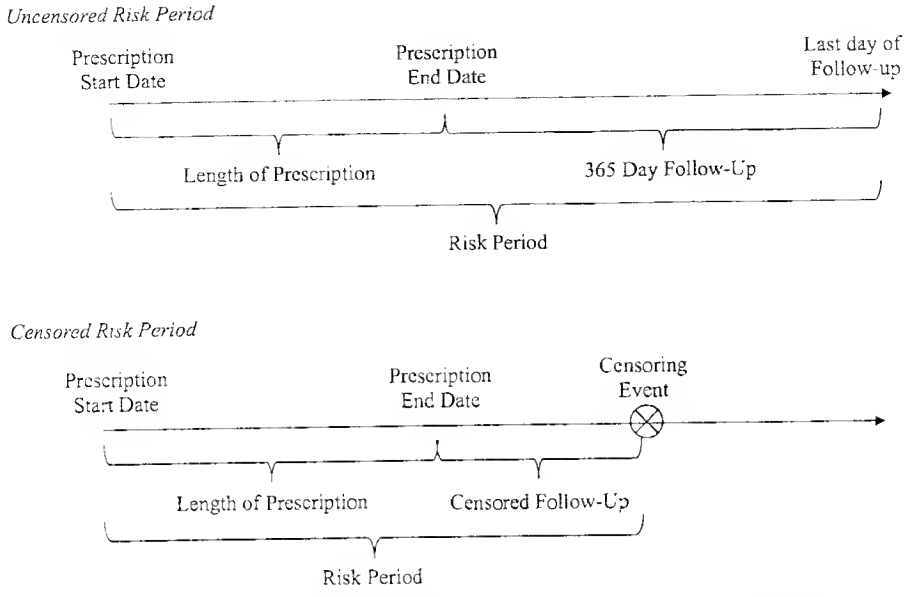

FIGURE 1. Schematic of uncensored and censored risk periods of follow-up. A censoring event was defined as having the outcome of interest, switching antimalarial medications, switching to a reserve component, leaving military service, or death.

complete capture of medical events before 2008, the study time period was restricted to begin in 2008.

The risk period for NPOs was defined as the entire duration of the prescription plus 365 days after the end of the prescription (Figure 1). If an individual had overlapping or back-to-back prescriptions, the risk periods were merged. A risk period was censored when an individual had the outcome of interest, switched to a reserve component, left military service, or died. Additionally, mefloquine risk periods were censored if the service member received doxycycline or A/P during the risk period (0.06% of mefloquine prescriptions). For objective 1, service members could have multiple risk periods if they received multiple antimalarial prescriptions during the study period.

Since deployment could be a confounder for many of the outcomes of interest, each antimalarial cohort was stratified into deployed and nondeployed cohorts for objective 1. Deployment was defined as being in a deployed setting according to the DoD Contingency Tracking Roster. A risk period was categorized as deployed if the prescription was filled within 30 days before the start of a deployment or if the risk period overlapped with a deployment. Since the nondeployed cohort was prescribed antimalarial medication, the assumption was made that these subjects were traveling to malaria-endemic areas for nonofficial or off-duty business or vacation/personal reasons, separate from a documented deployment.

Ascertainment of neuropsychiatric adverse events. Ambulatory and inpatient medical encounters occurring in theater or at fixed medical facilities during a risk period were searched for International Classification of Disease–Clinical Modification, 9th Revision (ICD-9-CM) codes for an NPO. A variety of case definitions were used depending on the outcome of interest (Table 1).[19–21] Completed suicide was identified using the casualty data in DMSS with suicide listed as the manner of death. For each outcome, the

TABLE 1

Case definitions for neuropsychiatric diagnoses

Diagnosis	ICD-9-CM codes	Case definition
Adjustment disorders	309.XX (excluding 309.81)	One hospitalization, at least two ambulatory encounters within 180 days of each other, or at least one ambulatory encounter in a psychiatric or mental health-care specialty setting with the diagnosis of interest in the first or second diagnostic position
Anxiety disorders	300.0X, 300.2X, 300.3X	
Depressive disorders	296.2X, 296.3X, 296.9, 296.90, 296.99, 311.XX	
PTSD	309.81	
Psychoses*	297.XX, 298.XX, 293.81, 293.82	At least one ambulatory or hospitalization with the diagnosis of interest in any diagnostic position
Tinnitus	388.3	
Vertigo	386.1, 386.2, 780.4	
Suicide ideation	V62.84	
Convulsions	780.3, 780.39	
Hallucinations	780.1	
Paranoia*	297.0, 297.9, 298.3	
Confusion*	298.2	
Insomnia	307.41, 307.42, 327.00, 327.01, 372.02, 327.09, 780.52	At least one hospitalization or at least two ambulatory encounters within 90 days of each other with the diagnosis of interest in any diagnostic position

ICD-9-CM = International Classification of Disease–Clinical Modification, 9th Revision; PTSD = posttraumatic stress disorder.
*The ICD-9-CM codes for paranoia and confusion are also contained in the ICD-9-CM code group for psychosis. However, these diagnoses were looked at individually using a separate case definition than psychosis.

incident encounter was defined as the first medical encounter during military service. Objective 1 included only incident encounters in the analysis; for the psychiatric outcomes (adjustment disorder, anxiety disorder, depressive disorder, PTSD, psychosis, suicide ideation, paranoia, and confusion), subjects were excluded if they had a medical encounter for any of the psychiatric outcomes before entry into the study cohort.

Statistical analysis. Descriptive statistics were generated for each cohort. For objective 1, incidence rates (IRs) and 95% confidence intervals (CIs) for each NPO were calculated for each cohort. The denominator was person-years (py) accrued during each risk period. Poisson regression models were used to calculate incidence rate ratio (IRR) and 95% CI comparing the mefloquine cohorts to the doxycycline and A/P cohorts. Models were adjusted for age, sex, service, grade, and year of prescription start. Deployed cohort models were additionally adjusted for deployment location (Afghanistan, Iraq, Africa, or other) and combat exposure. Combat exposure was defined as positively responding to at least one of three questions (encountering dead bodies or seeing people killed or wounded, engaged in direct combat where weapon was discharged, or felt in danger of being killed) on the Post-Deployment Health Assessment DD2796 form for the deployment of interest.[22] A secondary analysis additionally stratified the cohorts by sex.

Multiple sensitivity analyses were conducted for objective 1 and included the following: 1) including only the first risk period in the analysis, 2) restricting to hospitalized NPOs, 3) using all diagnostic positions for each NPO case definition, 4) stratifying cohorts by history of traumatic brain injury, and 5) restricting the risk period to 30 days after the end of the prescription. However, none of these analyses significantly changed the results of the study and are therefore not reported.

Objective 2 was restricted to the first prescription per individual and included individuals with a prior history of an NPD. The percentage of mefloquine and doxycycline subjects with a medical encounter for an NPD during the 365 days before the start of the prescription was calculated. IR and IRR and 95% CI for each outcome comparing those with and without a prior history were calculated for the mefloquine and doxycycline cohorts separately. The A/P cohort was excluded from this objective due to insufficient sample size. Ratios of rate ratios (RRRs) were calculated comparing the mefloquine IRR to the doxycycline IRR (N. P. Klein, 17th Annual Conference on Vaccine Research, April 2014). Permutation tests were conducted to determine the statistical significance of the RRR; the nonparametric percentile bootstrap method was used to generate the 95% CI.[23–28]

SAS 9.4 (SAS Institute Inc., Cary, NC) was used for the analysis. The study was designated as public health practice by the U.S. Army Public Health Command Public Health Review Board and the Army Human Research Protections Office.

RESULTS

Cohort characteristics. A total of 36,538 individuals were included in the mefloquine cohort. The doxycycline cohort consisted of 318,421 individuals, whereas the A/P cohort consisted of 12,881 individuals (Table 2). The mefloquine and doxycycline cohorts were comparable except for service, grade, and year of prescription. Mefloquine recipients were more likely to be Air Force members(58%), senior enlisted (47%), and to have filled the prescription in 2008 or 2009 (75% combined), whereas doxycycline recipients were primarily Army members (69%), junior enlisted (48%), and filled prescriptions during 2010 or later (78% combined). The A/P cohort differed from the other two cohorts on several demographics; this cohort was older, equally distributed among Army, Navy, and Air Force members, more likely to be senior enlisted or officers, filled the prescription in 2012 or 2013, and less likely to be deployed (20%). Among deployed subjects, 29%, 43%, and 21% reported combat exposure for the mefloquine, doxycycline, and A/P cohorts, respectively.

Risk of neuropsychiatric outcomes. Table 3 provides the counts and crude IR for each NPO by deployed and nondeployed drug-specific cohorts. Among all deployed cohorts, adjustment disorder was the most common outcome and had the highest crude IRs (13.60–56.92 per 1,000 py) (Table 3). The next three most frequent diagnoses among the deployed cohorts included insomnia (15.78–27.53 per 1,000 py), anxiety disorder (14.51–23.53 per 1,000 py), and tinnitus (10.24–18.25 per 1,000 py). Between nondeployed cohorts, there was no consistency in the most frequent outcomes.

IRRs comparing mefloquine to doxycycline for both deployed and nondeployed cohorts revealed statistically significant reduced risks for a large number of outcomes (Table 4). However, after adjustment, these outcomes were no longer statistically significant for the deployed cohort. Among the deployed cohorts, anxiety disorder had an elevated adjusted IRR of 1.12 (95% CI = 1.01–1.24) comparing mefloquine to doxycycline. Among the nondeployed cohorts, the adjusted IRRs for adjustment disorder, insomnia, anxiety disorder, depressive disorder, vertigo, and PTSD all remained statistically significantly protective for mefloquine compared with doxycycline. Among the nondeployed cohorts, the mefloquine cohort did not demonstrate a significantly elevated risk for any outcome. When comparing the mefloquine cohorts to the A/P cohorts for both deployers and nondeployers, tinnitus had a statistically significant elevated adjusted IRR (Table 5). The adjusted IRR was 1.81 (95% CI = 1.18–2.79) and 1.51 (95% CI = 1.13–2.03) for the deployed and nondeployed cohorts, respectively. Additionally, the IRR for PTSD was statistically significantly elevated among the nondeployed cohort (IRR = 1.83 [95% CI = 1.07–3.14]).

Similar results were seen when the cohorts were stratified by sex. There were no differences in the IRR for any of the outcomes between males and females (data not shown).

History of neuropsychiatric diagnoses and subsequent risk. Overall, 5.9% of the mefloquine cohort had at least one NPD in the year before prescription, compared with 9.2% in the doxycycline cohort (Table 6). The most frequent prior diagnosis for both cohorts was adjustment disorder (mefloquine: 2.1%; doxycycline: 4.6%). The proportion of mefloquine subjects with an NPD in the year prior was stable from 2008 to 2010 (5.7%), but increased to 10.8% in 2012 and 8.0% for the partial 2013 year (Figure 2).

TABLE 2
Characteristics of antimalarial medication study cohorts

Demographic	Mefloquine		Doxycycline		Atovaquone/proguanil	
	N	%	*N*	%	*N*	%
Total	36,538	100	318,421	100	12,881	100
Age (years)						
17–19	831	2	16,116	5	143	1
20–29	19,814	54	192,920	61	5,139	40
30–39	11,494	31	82,433	26	4,820	37
40+	4,399	12	26,952	8	2,779	22
Sex						
Female	5,589	15	36,913	12	1,975	15
Male	30,949	85	281,508	88	10,906	85
Service						
Army	9,521	26	219,897	69	4,387	34
Navy	3,623	10	21,992	7	3,376	26
Air Force	21,185	58	58,537	18	4,168	33
Marine Corps	2,138	6	16,959	5	677	5
Coast Guard	71	0	1,036	1	273	2
Grade						
Junior Enlisted (E1–E4)	11,955	33	152,110	48	2,451	19
Senior Enlisted (E5–E9)	17,160	47	107,692	34	4,872	38
Junior Officers (O1–O3/W1–W3)	4,339	12	40,693	13	2,546	20
Senior Officers (O4–O9/W4–W5)	3,084	8	17,926	5	3,012	23
Year of prescription						
2008	13,610	37	22,094	7	1,331	10
2009	13,753	38	46,713	15	1,407	11
2010	6,307	17	80,471	25	1,247	10
2011	1,852	5	74,432	23	1,772	14
2012	705	2	67,071	21	3,793	29
2013	311	1	27,640	9	3,331	26
Deployed during risk window						
No	10,847	30	71,635	23	10,261	80
Yes	25,691	70	246,786	77	2,620	20
Combat exposed (deployed only)						
No	13,876	54	108,171	44	1,492	57
Yes	7,482	29	106,967	43	539	21
Missing	4,333	17	31,648	13	589	22

For both the mefloquine and doxycycline cohorts, individuals with an NPD in the year prior had a statistically significant elevated risk for a subsequent diagnosis of the same condition compared with individuals without that diagnosis in the year prior (Table 7). This was true for all outcomes investigated in the analysis. The adjusted IRR for the mefloquine cohort ranged from 4.32 (95% CI = 3.15–5.93; vertigo) to 122.7 (95% CI = 51.42–292.78; convulsions). The adjusted IRR for the doxycycline cohort ranged from 4.86 (95% CI = 4.73–5.00; adjustment disorder) to 134.80 (95% CI = 110.13–164.99; convulsions). The RRR point estimates were equal to or greater than 1.00

TABLE 3
Number and IR of neuropsychiatric outcomes by antimalarial medication cohort and deployment status

Outcome	Mefloquine				Doxycycline				Atovaquone/proguanil			
	Deployed		Nondeployed		Deployed		Nondeployed		Deployed		Nondeployed	
	N	IR*	*N*	IR*	*N*	IR*	*N*	IR*	*N*	IR*	*N*	IR*
Adjustment disorder	977	28.66	243	18.75	21,154	56.92	3,699	44.35	88	31.61	156	13.60
Insomnia	598	15.78	145	10.09	11,895	27.53	2,193	22.46	76	23.21	136	10.74
Anxiety disorder	499	14.51	121	9.28	8,948	23.53	1,569	18.47	42	14.97	100	8.69
Tinnitus	509	13.44	198	14.02	7,925	18.25	1,491	15.17	34	10.24	141	11.27
Depressive disorder	429	12.46	112	8.59	7,090	18.59	1,550	18.24	20	7.09	79	6.86
Vertigo	443	12.19	165	11.90	6,340	14.85	1,494	15.75	36	11.24	138	11.42
PTSD	382	11.08	66	5.05	5,944	15.55	775	9.06	19	6.74	44	3.81
Suicide ideation	71	2.05	20	1.53	1,703	4.43	363	4.23	2	0.71	17	1.47
Convulsions	40	1.03	25	1.71	753	1.67	220	2.16	8	2.31	9	0.69
Psychoses	11	0.32	6	0.46	321	0.83	60	0.70	0	0	2	0.17
Hallucinations	4	0.10	1	0.07	198	0.44	39	0.38	2	0.58	5	0.38
Paranoia	2	0.06	0	–	33	0.09	11	0.13	0	–	0	–
Suicide	1	0.03	1	0.08	11	0.03	4	0.05	0	–	1	0.09
Confusion	0	–	1	0.08	10	0.03	4	0.05	0	–	0	–

IR = incidence rate; PTSD = posttraumatic stress disorder.
*Per 1,000 person-years.

TABLE 6

Number and percentage of subjects in the mefloquine and doxycycline cohorts with a neuropsychiatric outcome diagnoses in the 1 year before the first antimalarial prescription

	Mefloquine		Doxycycline	
Outcome*	N	%	N	%
Adjustment disorder	764	2.1	14,614	4.6
Anxiety	341	0.9	5,652	1.8
Insomnia	253	0.7	3,371	1.1
Depressive disorder	359	1.0	6,390	2.0
PTSD	131	0.4	2,671	0.8
Tinnitus	332	0.9	3,239	1.0
Vertigo	460	1.3	3,997	1.3
Suicide ideation	17	0.1	844	0.3
Convulsions	32	0.1	375	0.1
Psychosis	7	0.0	125	0.0
Hallucinations	1	0.0	41	0.0
Any†	2,164	5.9	29,405	9.2

PTSD = posttraumatic stress disorder.
*Outcomes not listed were not diagnosed in the 365 days before prescription.
†Individuals with a prior history of multiple outcomes are only counted once in the "Any" category

diagnosed with an NPO.[15,17,30] Contrary to our findings, other studies have reported an association between NPOs and mefloquine.[6,10,11,13,31–33] The study by Schlagenhauf and others was a randomized, double-blinded study among travelers and found mefloquine to have the highest proportion of moderate to severe NPOs compared with chloroquine/proguanil, doxycycline, and A/P.[6] However, this study had small numbers and the outcomes were defined by a subjective questionnaire as opposed to medical diagnoses of the outcomes.

The finding of similar IRRs for males and females is contrary to other studies which found females to have higher risks of NPOs than males.[6,8,10,31,34] However, this difference may be explained by factors such as entrance screening for mental health issues, physical fitness requirements, and combat exposures that distinguish military females from the general female population.

Among individuals with a prior history of an NPD, the study did not identify a statistically significant increased risk for subsequent diagnoses of the same condition among mefloquine subjects compared with doxycycline subjects.

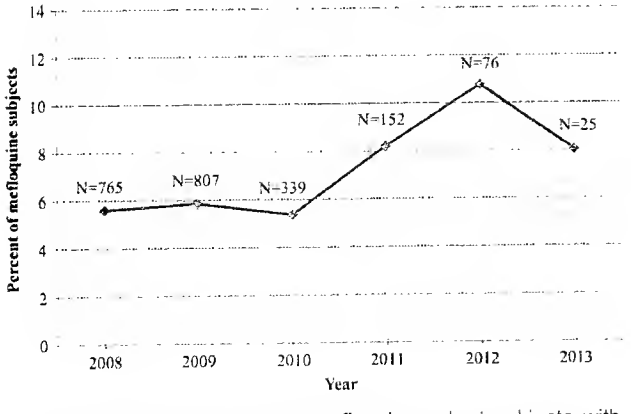

FIGURE 2. Percentage of the mefloquine cohort subjects with a neuropsychiatric outcome diagnosed in the 1 year before first mefloquine prescription by year of prescription start. *Data for 2013 is only through June 30, 2013.

However, nonsignificant elevated risks of four outcomes and nonsignificant decreased risks for three outcomes were seen. It is likely that, with a larger sample size, anxiety (higher risk) and vertigo (lower risk) might reach statistical significance. Van Riemsdijk and others reported more definitive findings in a Dutch study which evaluated the risk of serious psychiatric events while taking mefloquine, reporting more than double the risk of a psychiatric event in those with versus without a history of psychiatric disease.[10] Findings like these and those of other studies are the basis for the mefloquine package insert statement that a history of psychiatric illness is a contraindication for use of the drug.[29]

This issue is especially relevant for the military since the proportion of mefloquine prescriptions to individuals with NPOs in the year prior has nearly doubled since 2010. However, it should be noted that not all of the NPOs investigated in this study are classified as contraindications to mefloquine. Before 2011, the percent of mefloquine recipients with a prior NPO diagnosis was similar to the percentage of mefloquine recipients with a contraindication reported among U.S. military deployers to Afghanistan in 2007 (4.8%), but lower than the percentage of contraindications reported among U.S and United Kingdom civilians (7.5–9%).[35–37] In 2012 and 2013, prior NPO diagnoses among mefloquine recipients were higher than any of these previous reports. This rising proportion of mefloquine prescriptions for individuals with a history of NPOs suggests the potential need for improved scrutiny of each service member's medical history before prescribing mefloquine. It may be beneficial to implement patient alert cards for contraindication before being able to prescribe mefloquine.

The findings of this study should be interpreted in light of its limitations. The use of electronic medical data archived in DMSS allowed for near complete capture of diagnoses recorded during medical encounters; however, these data are dependent upon the accuracy of ICD-9 coding. These data may be inaccurate due to miscoding, may reflect "rule out" diagnoses or may be subject to other error. In an effort to minimize some of these potential issues, standardized case definitions were used and typically required more than one encounter for the same medical condition. Additionally, service members may have experienced outcomes for which they never sought medical care, or received care from sources not documented in DMSS. Such outcomes would not be captured in the analysis and would result in under-ascertainment of the NPOs. It is not expected that such misclassification of the outcome would differ by drug type, making the misclassification nondifferential and biasing the results toward the null. Some medical care administered to deployed personnel at level 1 or role 1 facilities (immediate first aid delivered at the scene/Battalion Aid Stations), may also not be captured in the electronic medical data. This may result in under-ascertainment of NPOs treated in a level 1 or role 1 facility. Given the 365-day postprescription follow-up period, it is expected that persistent and more severe NPOs will get captured from medical care administered after return from deployment. Additionally, anecdotal reports indicate that antimalarial medications were provided to entire deploying units for force health protection measures and were not documented as an individual medical prescription. If this occurred, there is no way

TABLE 7

IRR of each neuropsychiatric outcome comparing individuals with a 1-year prior history to those without: stratified and comparing mefloquine and doxycycline

	Diagnosis vs. no diagnosis of the condition in the 1 year before antimalarial medication		Mefloquine IRR compared with doxycycline IRR	
	Mefloquine cohort	Doxycycline cohort		
Outcome*	Adjusted IRR (95% CI)†	Adjusted IRR (95% CI)†	Bootstrap RRR (95% CI)	Permutation test *P* value
Adjustment disorder	5.47 (4.69–6.36)	4.86 (4.73–5.00)	1.13 (0.94–1.34)	0.81
Anxiety	16.95 (13.86–20.73)	13.50 (12.92–14.11)	1.26 (0.98–1.59)	0.17
Insomnia	7.62 (5.57–10.44)	6.66 (6.20–7.15)	1.14 (0.80–1.59)	0.61
Depressive disorder	12.54 (10.04–15.67)	12.58 (12.04–13.14)	1.00 (0.78–1.29)	0.38
PTSD	27.98 (20.71–37.82)	24.60 (23.17–26.12)	1.14 (0.78–1.65)	0.88
Tinnitus	7.52 (5.70–9.91)	8.05 (7.43–8.71)	0.93 (0.69–1.23)	0.60
Vertigo	4.32 (3.15–5.93)	5.90 (5.39–6.46)	0.73 (0.50–1.00)	0.06
Convulsions	122.7 (51.42–292.78)	134.80 (110.13–164.99)	0.91 (0.25–2.34)	0.73

CI = confidence interval; IRR = incidence rate ratio; PTSD = posttraumatic stress disorder; RRR = ratio of rate ratios.
*Outcomes not listed were not diagnosed in the 365 days before prescription.
†Models adjusted for age, sex, service, grade, year of prescription start, deployment status.

to capture those prescriptions and this study is missing those individuals in the analysis. However, the risk of developing NPOs among the group with undocumented prescriptions is not expected to be different than the risk among service members given an actual prescription. Temporal trends in deployment locations, combat exposure, and type of antimalarial medication prescribed had the potential to confound these results. However, we attempted to account for these factors by adjusting our models by year of prescription start and deployment status, location, and combat exposure.

Potentially one of the most significant limitations of this study is the lack of data on prescription compliance. Service members were assumed to have taken the prescription in its entirety; however, it is unlikely that complete chemoprophylaxis adherence was achieved. Self-reported compliance with antimalarial medications among military personnel was found to be 60% among a group of Afghanistan deployers, and in one report, self-reported compliance for mefloquine (48.5%) was much lower than for doxycycline (78.4%) and other antimalarials.[38,39] However, other studies have found that compliance with mefloquine is higher than with doxycycline (American Soldiers: 80% versus 60%; Turkish troops: 61% versus 56%; Australian travelers: 78% versus 68%).[40–42] However, how compliance is defined is important in interpreting these findings. In the cited studies, estimated compliance rates correspond to taking the medication as prescribed without missing a dose. This is different than completely stopping the medication, which was only reported between 3% and 5% for either medication among service members.[41,42] Complete cessation of the medication would impact this study more profoundly than missing doses, but this is also expected to occur among a small percentage of subjects. If subjects stopped taking prescribed prophylaxis due to adverse events and if the adverse events resulted in a medical encounter, then it would have been captured and the risk period would have been censored appropriately. However, if the adverse events were not reported and the individual did not switch antimalarial medications, then the risk period would have been overestimated.

A strength of this analysis is the large sample size which allowed for investigation of NPOs which are infrequently diagnosed (i.e., "rare" outcomes). However, some outcomes were so infrequent (e.g., suicide), that estimates derived for these outcomes may be unreliable. The use of robust statistical methods allowed for complex comparisons between subcohorts of the mefloquine and doxycycline cohorts. Use of the electronic medical encounter and pharmacy data allowed for near complete capture of medical encounters and removed potential reporting bias.

In summary, on a population level, this study did not find an association between mefloquine and NPOs among U.S. military service members, with the exception of anxiety, tinnitus, and PTSD for some subcohorts. Among service members with a history of an NPD during the year before beginning chemoprophylaxis, mefloquine was associated with an increased risk of subsequent diagnosis of the same outcome. These findings emphasize the need for appropriate screening for contraindications when physicians prescribe mefloquine.

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September 20, 2019

Dr. Remington Nevin
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Re: Freedom of Information Act (FOIA) Appeals 2016-010, 2016-064

Dear Dr. Nevin:

The Defense Health Agency (DHA) received your letters on August 15, 2019, regarding the status of your appeals under the Freedom of Information Act (FOIA), numbered 2016-010 and 2016-064. I responded to these appeals last summer. The copies of the responses are enclosed.

My understanding was you resolved other FOIA appeals by working directly with DHA FOIA contract employees to find the information. If you have additional open appeals, please forward them to me directly at paul.t.cygnarowicz.civ@mail.mil. Thank you.

If you have any questions on processing your requests under the FOIA, please contact Ms. Nadine Brown at the Defense Health Agency Privacy and Civil Liberties at (703) 275-6009.

Sincerely,

Paul Cygnarowicz

Paul Cygnarowicz
FOIA Appellate Authority
DHA Office of General Counsel

Encl
1. Appeal Response 2016-010
2. Appeal Response 2016-064